Vaccine safety segment from Immunization Update satellite broadcast, August 15, 2002

Written by William Atkinson, MD, Ray Strikas, MD, and Donna Weaver, MN, National Immunization Program, Centers for Disease Control and Prevention.

In this segment of today's program we would like to discuss two recent vaccine safety reports by the Immunization Safety Review Committee of the Institute of Medicine. Before we talk about the specific reports, it's useful for you to know a little background on the Institute of Medicine and their vaccine safety activities.

The Institute of Medicine, or IOM, is part of the National Academy of Sciences, a private, nonprofit society of scientists and researchers. The National Academy of Sciences was granted a charter by Congress in 1863, and was mandated to advise the federal government on scientific and technical matters. The Institute of Medicine was established by the National Academy of Sciences in 1970 to advise the federal government on issues related to the health of the public. IOM also acts independently to identify important issues of medical care, research and education.

The IOM has a long history of involvement in vaccine safety. It issued 4 major reports on this subject between 1977 and 1994, and has conducted several smaller studies and workshops focused on various vaccine safety topics.

In 2000, CDC and the National Institutes of Health requested that IOM establish an independent expert committee to review the available evidence on a series of immunization safety concerns. The Immunization Safety Review Committee is made up of 15 members with expertise in a variety of medical fields, nursing, epidemiology, biostatistics and ethics.

Because of the sensitive nature of this subject, IOM established strict criteria for committee membership to minimize concerns about conflict of interest. These criteria prevented participation by anyone with financial ties to vaccine manufacturers or their parent companies, previous service on major vaccine advisory committees, or prior expert testimony or publications on issues of vaccine safety.

The first Immunization Safety Review Committee report- which addressed measles mumps rubella vaccine and autism- was released in April 2001. The second report on thimerosal

containing vaccines and neurodevelopmental disorders was released in October 2001. In February, 2002, the committee released its third report which addressed multiple immunizations and immune dysfunction, and released its fourth report in May, 2002, on hepatitis B vaccine and demyelinating disorders.

For each hypothesis that is examined, the committee assesses both the scientific evidence and the issue's significance to society. For these reviews, the scientific assessment has two parts: an examination of evidence that the hypothesis is biologically plausible; and an examination of the evidence for a causal relationship between the vaccine and the adverse event.

In looking at the significance to society, the committee includes a review of health risks associated with the vaccine preventable disease and with the adverse event in question and other societal concerns. The findings of the scientific and significance assessments provide the basis for the committee's recommendations. The Immunization Safety Review Committee uses a framework for assessing causality used for reviews of vaccine safety in 1991 and 1994.

The categories of causal conclusions are: no evidence; evidence is inadequate to accept or reject a causal relationship; evidence favors rejection of a causal relationship; evidence favors acceptance of a causal relationship; and evidence establishes a causal relationship. The most definitive category is "establishes causality", which is reserved for those relationships where the causal link is unequivocal. An example of this is the association of oral polio vaccine and vaccine associated paralytic polio. "Favors rejection" is the strongest category in the negative direction. Notice that the committee does not include a category of "establishes no causal relationship". This is because it's virtually impossible to prove the ABSENCE of a relationship with the same certainty that is possible in establishing its presence. That is, it's very difficult to prove "NEVER". The "no evidence" category means there is a complete absence of clinical or epidemiological evidence, rather than meaning that no causal relationship has been shown.

Committee assessments begin from a position of neutrality regarding the specific vaccine safety hypothesis under review. That means there is no presumption that a specific vaccine or vaccine component does or does not cause the adverse event in

question. The weight of the available evidence determines whether it's possible to move from that neutral position to a finding FOR causality or AWAY FROM causality. This is different than in a typical scientific study in which the hypothesis is that there is NO relation, and evidence must be sufficient to reject that hypothesis.

Multiple vaccinations and immune system dysfunction

Although most people realize the benefits of vaccinations, a recent survey showed that approximately one quarter of parents believe that infants get more vaccines than are good for them, and that too many immunizations could overwhelm an infant's immune system. Because immune system dysfunction is a broad term, the committee focused its review on the following questions: do multiple immunizations have short-term effects on developing infants' immune systems that leave them susceptible to other infections? Does exposure to multiple vaccines directly and permanently redirect the immune system toward autoimmunity, as reflected in type 1 diabetes? And does exposure to multiple vaccines directly and permanently redirect the immune system toward allergy, as reflected in asthma?

In order to conduct their review, the committee focused on defined conditions like diabetes mellitus and asthma for which studies can be reviewed and compared, as opposed to vaguely defined, atypical or non-specific conditions. The main concern about multiple immunizations is whether an infant's immune system is overloaded by all the vaccines on the recommended immunization schedule. This concern has increased as the number of recommended vaccines has increased.

The committee found that the number of antigens in the recommended childhood immunization schedule actually has decreased in the past 30 years, even though the number of vaccines and vaccine doses has increased. This decrease is due to removal of smallpox and whole cell pertussis vaccines from the childhood immunization schedule, which eliminated 200 and 3 thousand antigens, respectively. The committee also reviewed estimates that suggest the capacity of the infant immune system is at least 1000 times greater than what is required to respond to immunizations.

The committee examined the so-called hygiene hypothesis. This hypothesis suggests that because we live in cleaner environments our immune systems are weaker today than they were in the past. The committee's report points out that the

potential role of vaccine preventable diseases as part of the hygiene hypothesis is minimal. In fact, the number of infections prevented by immunization is actually quite small compared with the number prevented by other interventions such as clean water, food, and living conditions. The committee concluded that this mechanism is only theoretical and if proven, immunizations would play an insignificant role.

The IOM Immunization Safety Review Committee's most important conclusions were that the available scientific evidence does not support the hypothesis that the infant immune system is inherently incapable of handling the number of antigens that children are exposed to during routine immunizations. There is evidence for the existence of biological mechanisms by which multiple immunizations could possibly influence an individual's risk for infections. But the epidemiologic evidence- that is, data from studies of vaccine exposed populations and their control groups- favors rejection of a causal relationship between multiple immunizations and increased risk for infections or for type 1 diabetes mellitus. Finally, the epidemiologic evidence regarding increased risk for allergic disease, particularly asthma, was inadequate to accept or reject a causal relationship.

The Committee recommended limited but continued public health attention to this issue in the form of policy analysis and communication strategy development. They recommended and endorsed a number of research activities, including the use of existing vaccine safety monitoring systems to study questions related to asthma and other allergic disorders, as well as diabetes mellitus and other important autoimmune diseases. The Committee did NOT recommend a review by national and federal vaccine related advisory groups of the licensure or schedule of administration of vaccines on the basis of concerns about immune dysfunction.

These recommendations will be considered in depth by Public Health Service agencies during the next several months.

Hepatitis B and autoimmune disease

ACIP and other advisory committees recommend hepatitis B vaccination for all infants, adolescents and high risk adults. These recommendations have been viewed with skepticism by some people because of concerns about the safety of the vaccine, and because of a perception that hepatitis B infection is not a serious risk to the general population.

The Immunization Safety Review Committee released a report in May 2002 that addressed the relationship between hepatitis B vaccine and several demyelinating neurological disorders. The disorders included multiple sclerosis, optic neuritis, acute disseminated encephalomyelitis, transverse myelitis, Guillain Barre Syndrome and brachial neuritis. The committee focused on these conditions because they are serious neurological disorders and known clinical entities. In addition, published epidemiological studies and case reports are available that investigated the association of some of these diseases with hepatitis B vaccine, and a substantial amount of literature exists on the pathophysiology of several of these conditions. Most of the epidemiological evidence examined by the committee concerned the connection between hepatitis B vaccination and the diagnosis of MS, or the risk of a relapse in patients previously diagnosed with MS.
Multiple sclerosis is the most common inflammatory demyelinating disease of the central nervous system in humans. Approximately 300,000 people, or about 0.1% of the population, have been diagnosed with the disease in the United States. Women are affected about twice as often as men. The incidence of the disease is highest in persons between 20 and 40years of age, but it has been diagnosed in children as young as 2 years, and in older people. The severity of the disease is variable, and can range from subclinical forms that are diagnosed only after death from other causes to hyperacute forms that lead to death within the first few months after onset. The cause of multiple sclerosis remains elusive, but susceptibility appears to involve both genetic and environmental factors. 2 to 5 percent of fraternal twins and other siblings of persons with MS will be affected. But 30 to 35 percent of monozygotic or identical twins will be affected if the other twin has the disease.

The committee concluded that there is at least a theoretical basis for the hypothesis that vaccines, including hepatitis B vaccine, could cause demyelinating disorders. The details of these immunologic mechanisms are beyond the scope of this program, but basically involve the destruction of nerve tissue through the development of antibody to myelin following vaccination. Another possible mechanism is the release of inflammatory mediators such as cytokines following vaccination that could participate in the demyelination process. But the biologic evidence for these mechanisms is weak.

From the data reviewed, the Committee concluded that the evidence favors rejection of a causal relationship between

hepatitis B vaccine administered to adults and either onset or relapse of multiple sclerosis. There are no epidemiological data regarding the relationship of hepatitis B vaccination in infants and young children and the risk for MS. The Committee could not extend the causality conclusion based on studies in adults to include a possible risk to infants and young children.

The Committee concluded that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and all other demylenating conditions, such as optic neuritis, transverse myelitis, and Guillain Barre syndrome.

Overall, the committee found little indication that safety concerns are a major barrier to acceptance of hepatitis B vaccination in the United States. This is evident from National Immunization Survey data that showed 90 percent vaccination coverage among children 19 to 35 months of age in 2000. But the committee also concluded that concerns about hepatitis B vaccine remain significant for some parents and workers who are required to take the vaccine because of occupational risk.
The Immunization Safety Review Committee did NOT recommend a policy review of hepatitis B vaccine by any of the national and federal vaccine advisory bodies on the basis of concerns about demyelinating neurological disorders. Among other things, the committee recommended surveillance of multiple sclerosis and other central and peripheral nervous system demyelinating disorders, specifically in health care workers and those born since 1991. They also recommended further public health attention on the issue in the form of additional research and communications to increase understanding of the basis for hepatitis B recommendations in the United States.

Both of these Institute of Medicine reports on vaccine safety are excellent reviews, and we recommend that all vaccination providers familiarize themselves with them. These, as well as the earlier reports on MMR and autism, and thimerosal containing vaccines are available on the National Immunization Program website. We will give you the address at the end of the broadcast.